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### Health Outcome Prioritization in Alzheimer's Disease

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## **Health outcome prioritisation in Alzheimer's disease:**

### **Understanding the ethical landscape**

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# **ABSTRACT**

## ***Background***

Dementia has been described as the greatest global health challenge in the 21st century on account of longevity gains increasing its incidence, escalating health and social care pressures. These pressures highlight ethical, social, political challenges about healthcare resource allocation, what health improvements matter to patients, and how they are measured. This study highlights the complexity of the ethical landscape, relating particularly to the balances that need to be struck when allocating resources; when measuring and prioritising outcomes; and when individual preferences are sought.

## ***Objective***

Health outcome prioritisation is the ranking in order of desirability or importance of a set of disease-related objectives and their associated cost or risk. We analyse the complex ethical landscape in which this takes place in the most common dementia, Alzheimer's disease.

## ***Methods***

Narrative review of literature published since 2007, incorporating snowball sampling where necessary. We identified, thematised and discussed key issues of ethical salience.

## ***Results***

Eight areas of ethical salience for outcome prioritisation emerged: (1) Public health and distributive justice, (2) Scarcity of resources, (3) Heterogeneity and changing circumstances, (4) Knowledge of treatment, (5) Values and circumstances, (6) Conflicting priorities, (7) Communication, autonomy and Caregiver issues, (8) Disclosure of risk.

## ***Conclusion***

These areas highlight the difficult balance to be struck when allocating resources, when measuring and prioritising outcomes, and when individual preferences are sought. We conclude by reflecting on

how tools in social sciences and ethics can help address challenges posed by resource allocation, measuring and prioritising outcomes, and eliciting stakeholder preferences.

Keywords: Alzheimer Disease, Dementia, Health Priorities, Ethics

## INTRODUCTION

Health outcome prioritisation is the ranking in order of desirability or importance of a set of disease-related objectives and their associated cost or risk, obtained collaboratively with or from patients and their carers. It can occur at several levels and by different stakeholders, including: between a doctor [1], nurse [2], pharmacist [3] or other healthcare professional and an individual patient; within families of an individual or individuals with AD [4,5] between cohorts of patients and researchers in a Randomised Controlled Trial (RCT) [6]; by national healthcare systems such as the National Health Service (NHS) and associated resource allocation bodies such as the National Institute for Clinical and Care Excellence (NICE) [7]; and at the international level between governments when collaborating on meeting global health priorities [8]. Situations in which outcome prioritisation is useful include: i) regulatory scenarios for assessing benefit to risk ratio by, for example, establishing which endpoints would be the most relevant to measure in an RCT; ii) economic scenarios considering 'value for money', as the finitude of resources precludes being able to fund every intervention; iii) questions of individual benefit-to-risk ratios to establish what kind of care a particular patient wishes to receive.

Alzheimer's disease (AD) is the most common type of dementia and a '*global public health priority*'. [9,10] Some evidence suggests the prevalence of all-cause dementia rates may be declining [11], however with an ageing population and older people are living longer the incidence of specific dementias such as AD may continue to rise [12]. The prospect of a global prevalence of 131.5 million [11] imposes a significant and growing costs, necessitating innovation in the management of dementia [13].

In this paper we describe and analyse the evidence base for the complex ethical landscape of health outcome prioritisation as it takes place in the most common form of dementia, AD. The paper was produced as an Ethical, Legal, and Social Implications (ELSI) output for the European Union and Innovative Medicines Initiative (IMI)-funded consortium project, ROADMAP: Real World Outcomes across the AD spectrum for better care [14]. The authorial team is comprised of researchers working on the ROADMAP project, including clinicians, scientists, and patient representatives with expertise in AD, led by three bioethicists with expertise in analysing ethical issues in healthcare and medicine. Although there are several types of dementia, ROADMAP focuses exclusively on AD dementia; as such, the paper analyses ethical issues in health outcome prioritisation for AD alone. The research questions we seek to answer are:

- What are the ethical issues that drive outcome prioritisation?
- What balances need to be struck when prioritising outcomes?

Our analysis highlights eight key areas of ethical salience to fair outcome prioritisation in AD. There is currently no curative treatment for AD; as such, while we assume that if it were possible to cure AD, most individuals would be likely to prioritise this over other outcomes, since no cure exists, the review focuses on how outcomes other than this might be weighed and prioritised. The themes that emerged from our analysis illustrate the challenges of realising outcomes and making prioritisation choices. Given the growing global prevalence of AD analysis of these ethical issues is timely and necessary.

## **METHODS**

A narrative review based on a mixture of structured and ad-hoc searching of academic literature was conducted. This is a narrative, rather than systematic, review, capturing the landscape of the debate rather than surveying the prevalence of different views in the literature. While establishing the relative prevalence of different themes or theories would be independently interesting, our aim was the identification of these in the literature rather than their relative prominence. This choice reflects our

presumption that the normative legitimacy of ethical challenges is not a function of the frequency of their discussion.

Relevant manuscripts were identified in several stages. First, a structured search was carried out in January 2018 and updated in September 2019 across five academic indexes: EMBASE, PubMed (incl. MEDLINE), Scopus, Web of Science, and Google Scholar. The search identified articles with relevant titles using the search strings listed in Table 1.

Database	Search Strings	# Returned
<b>EMBASE</b>	[ethic* AND outcome*] AND [priorit* OR health* OR alzheimer* OR dementia*]	7
	[ethic* AND priorit*] AND [outcome* OR health* OR alzheimer* OR dementia*]	19
<b>PubMed [incl. MEDLINE]</b>	[ethic* AND outcome*] AND [priorit* OR health* OR alzheimer* OR dementia*]	7
	[ethic* AND priorit*] AND [outcome* OR health* OR alzheimer* OR dementia*]	21
<b>Scopus</b>	[ethic* AND outcome*] AND [priorit* OR health* OR alzheimer* OR dementia*]	10
	[ethic* AND priorit*] AND [outcome* OR health* OR alzheimer* OR dementia*]	23
<b>Web of Science</b>	[ethic* AND outcome*] AND [priorit* OR health* OR alzheimer* OR dementia*]	4
	[ethic* AND priorit*] AND [outcome* OR health* OR alzheimer* OR dementia*]	17
<b>Google Scholar</b> <i>[strings</i>	allintitle: [ethics OR ethical] AND [outcome OR outcomes] AND [prioritization OR prioritisation OR	11

<i>modified for compliance with search engine formatting]</i>	priority OR health OR healthcare OR health-related OR health-care OR alzheimer's OR alzheimer OR dementia]	
	allintitle: [ethics OR ethical] AND [prioritization OR prioritisation OR priority OR priorities] AND [outcome OR outcomes OR health OR healthcare OR health-related OR health-care OR alzheimer's OR alzheimer OR dementia]	18
<b>TOTAL</b> (Unique papers)		49

**Table 1 – Structured search results**

The keyword search was limited to the ‘Article Title’, for three reasons. First, a search of titles was likely to yield those articles most directly pertinent to our analysis. Second, additional snowball sampling via further references supplied by co-authors, and via screening of the references of already included studies identified further relevant research representing a broad range of stakeholders in AD,. Third, a preliminary search of abstracts as well as titles yielded an extremely large sample that, on the basis of screening a sample of the papers returned, added noise but little value in relation to capturing the principles of the ethical debate, when compared to the results of a title only search. This is to say that numerous papers are available which happen to use some of our keywords, but on reviewing are not pieces of research which are about ethics in any way that is relevant to our purpose. For example, a title and abstract search on SCOPUS for articles published in English for the specified date range using key terms ethic\* priorit\* and health\* returned 6820 documents.

To ensure a manageable and contemporary sample, we restricted our search to literature in peer-reviewed journal articles and conference proceedings published from 2007, ten years before work on the study began. Additionally, we only reviewed articles written in English. Article abstracts and, if needed, full texts were then assessed for relevance by a single reviewer. A subset of 20 articles was screened by a second reviewer, and the results of this screening by the two reviewers were compared for consistency in assessing the relevance of the study to the purposes of the review. This comparison

yielded an agreement of 85%, which indicated a reliable degree of consistency, and discussion of the reasons for the discrepancies in the remaining helped to refine shared understanding of the criteria when further screening was carried out. Finally, we screened the references of included articles to identify further relevant articles and allowed all authors to suggest further relevant articles not identified by the initial search (“snowball sampling”).

49 articles were retrieved by the initial search. 36 of these were rejected, either due to being judged insufficiently relevant after review; because they were irretrievable; or having been published in a language other than English, leaving 13 included and reviewed here. Snowball sampling and the introduction of additional previously collected articles of contextual relevance yielded a further 119 references, giving a total of 125 documents pertaining to ethical issues in outcome prioritisation in AD reviewed and discussed. Three references pertaining to research methodology were also provided for support in study design and data analysis.

Analysis of the papers aimed to map the landscape of prevalent ethical themes in the academic and clinical discussion around outcome prioritisation in healthcare generally and Alzheimer’s disease specifically. To identify themes for discussion, a pre-defined thematic framework was not used; rather, themes emerging from the literature were identified [15]. Each paper was read in full, key passages were highlighted that addressed ethical issues or concepts, understood here as areas of ‘right’ and ‘wrong’ or competing values and normative interests. Highlighted segments were labelled with codes reflecting the lead author’s interpretation of the text [16]. Our analytic approach was informed by established 'realist' and 'meta-narrative' methods of qualitative synthesis, drawing on previous ethics-focused review studies for guidance [17–19]. Discussion of the themes occurred between co-authors, who come from disciplines including philosophy, epidemiology, psychology and psychiatry, public health, as well as the pharmaceutical industry. Themes were reviewed and discussed at each draft iteration of the study until consensus was reached and there was agreement among all of the authors that the themes accurately reflected the findings of the analysis. This required five such iterations in total, at which point the thematic categorisation was finalised.



## RESULTS

Below, we outline eight areas of ethical salience in outcome prioritisation that emerged from the analysis. These eight areas are not themselves ranked in order of priority or importance; rather they reflect the landscape of matters of key ethical importance that arose from the review: (1) Public health and distributive justice, (2) Scarcity of resources, (3) Heterogeneity and changing circumstances, (4) Evidence, (5) Values and circumstances, (6) Conflicting priorities, (7) Communication, autonomy and caregiver issues, (8) Disclosure of risk.

### *Public Health and Distributive Justice*

A key ethical aspect of contemporary AD management is the shift towards public health prevention [10] away from clinical medicine [20], to contain the costs of supporting an expanding and ageing population in which AD prevalence will increase [21–23]. However the benefits of a preventive approach should not be overstated [20,24], rather, the benefits of promoting general health advice may extend to dementia [10]. This shift is important for determining an ethical prioritisation of outcomes in two respects.

First, public information about how to reduce the risk of dementia through lifestyle modifications from early life onwards affects the relationship between the state and its citizens [25]. Pressure to make certain choices may be viewed as an infringement of liberty [26,27], particularly where the state establishes policies that expect individuals to modify their behaviour; or prioritise treatment based on following preventative recommendations. Moreover, recommending lifestyle modifications that provide no guarantee to prevent AD may be viewed as unacceptably paternalistic and corrode trust.

Second, the application of Quality Adjusted Life Years (QALYs) to individual priorities may not adequately capture the subjectively bound nature of 'quality of life' or 'well-being', despite the centrality of both to ensuring a successful outcome for people with AD, given that personal evaluations of concepts such as these differ [28,29]. Furthermore, 'benefit' and 'value' may be interpreted differently. From a health economic perspective it is essential to attach a particular price to a particular level of benefit [30], however the priorities of individuals with AD are likely to differ

from other stakeholders, such as patients, their carers, health care professionals, providers, and payers of medical treatments [31].

### ***Scarcity of Resources***

Outcome prioritisation requires distributing limited resources to achieve desired outcomes. How these distribution decisions are made differs geographically. For example, in the UK, NICE prioritises cost-effectiveness, whereas cost-effectiveness does not inform decision-making in Germany, and in the Netherlands it informs decision-making but only above a certain price threshold (very cheap drugs do not attract scrutiny) [32].

Irrespective of particular metrics used, the finitude of resources means that some people will be denied access to interventions that would benefit them [33–35]. This is ethically significant since the needs of some will be de-prioritised in favour of the needs of others, and the resulting gap may conflict with the clinical duty of care (this also holds for prioritisation between people with the same condition and people with different conditions). As [36] summarises baldly, to prioritise is inevitably to say ‘no’ to somebody.

This is especially acute in the AD context, in which many people are unable to derive significant value, given that no curative treatments are yet available and evidence for the effectiveness of preventative interventions is weak. In light of this some have concluded that the greatest need is for high-quality long term care, and similarly high-quality support for family carers, such that the lives of people with AD and their families are made as satisfying as possible in the absence of any treatment that would decisively reverse the disease [5,37]. Indeed, research carried out by Kelly et al [2015, p. 990] [38] with people with dementia, their carers, clinicians, and other health professional finds preferences of this kind in the top ten overall prioritised outcomes across all groups.

Encouragingly, for the findings of our own analysis, there is also significant parity with the Kelly et al [Ibid.] study insofar as ethical dilemmas over finite resources report shared concerns, for example: negotiating the balance of benefits between pharmacological and lifestyle or social interventions; evaluating the value of early diagnosis in light of its psychological impact in the absence of a cure;

how to optimise outcomes for people with advanced dementia at the end of life; and how to also support carers of people with AD as well as people with AD themselves.

### ***Heterogeneity and Changing Circumstances***

Prioritisation decisions are ultimately concerned with both outcomes and endpoints, which are related but distinct parameters. Outcomes denote measured effects of treatment, whereas endpoints are pre-identified targets of a study built into its design [39]. From an international perspective, the outcomes and endpoints considered important may differ, depending on characteristics of particular markets [39]. Moreover, the definition, diagnostic cut-off and mechanism of measuring the numerous potential outcomes and endpoints continue to be debated; and the difficulty of determining preferences for these – for example living longer, declining more slowly, or dying sooner before more serious incapacity - is compounded by the plethora of available assessment tools. A further challenge in AD – and in the context of other conditions - is that assessment tools measuring a wide range of domains including memory, spatial orientation, semantic processing, speech, emotion, mood, apathy, aggression, mobility [40–42] are not ideally sensitive or specific and so do not yield perfect validity either in earlier and preclinical stages of the disease [40] or in more severe stages [41,42].

In addition to this heterogeneity in assessment tools, changing background circumstances also affect prioritisation decisions. Prioritisation is also made complex by the heterogeneity of AD itself, in that the disease affects different individuals in different ways, in different cultural contexts, and at different stages of the disease; indeed, priorities are likely to differ in line with the progression of the disease, since the impact of MCI, for example, is less severe than very advanced AD later in life [12,41]. As such the AD community itself cannot be assumed to be homogeneous with respect to how members of it are affected by the disease [42,43], which underlines the risk of assuming that the priorities of one AD population subgroup is necessarily representative of other subgroups or the AD population at large. Moreover, not only are resources for people with AD limited (as above), but their availability is not necessarily constant. For example, external or short-term political factors and election cycles can affect both health policy and budgets, which shape prioritisation decisions [44]. Equally, prioritisation is shaped by new advances in medical science that expand what is

therapeutically possible. Furthermore, global trends towards population growth and increasing life expectancy may mean a future in which more people are competing for fewer resources [45].

Outcome prioritisation should therefore be viewed as an *ongoing* process, requiring reflection and revision, according to changing circumstances, as needs and options change [46–48].

### ***Knowledge of Treatment***

Determining what counts as fair prioritisation of outcomes depends partly on what needs to be known to make the relevant decision [1,49]. Data from randomised trials is considered the ‘gold standard’ for establishing efficacy, however there are a number of challenges that make it expensive and time consuming to test the efficacy (or effectiveness) of a drug, and make it difficult to determine optimal clinical practice for long term treatment management in AD.

First, there is the challenge of attrition compromising the validity and / or generalisability of results from trials [50]. There is evidence that older, sicker individuals in particular are more likely to drop out of studies [51,52], die before the trial is concluded or to discontinue the study treatment due to adverse effects.

Second, people in symptomatic stages of AD are typically older and more likely to have comorbidities, making them complex [53–55]. RCTs of new drug products may investigate drug-drug interactions to some degree, but this is not always exhaustive. Data from RCTs about drug-drug combinations may be underpowered or simply unavailable. Since interventions may have trade-offs between desirable effects and undesirable side-effects, weighing these is less straightforward where comorbidities requiring different types of treatment are present [56]. Polypharmacy is common, without clinicians fully knowing the risk of harm due to lack of evidence. Indeed, separate studies are designed to address these issues [57], and knowledge of the mechanism of action of certain drugs contributes usefully to decision-making. Notwithstanding the challenges outlined, therefore, clinicians are not *uninformed* when prescribing certain drugs. Rather, the biggest challenge arises when patients have multiple comorbidities which all require treatment [58] since it may become necessary to prioritise the treatment of some rather than other in order to realise an all-things-considered, rather

than ideally, desirable outcome. As such, ensuring an optimal balance of outcomes in the context of chronic disease in old age is particularly challenging [59]. This uncertainty poses a further challenge for realising priority outcomes which depend on the effectiveness of a particular drug.

### ***Values and Circumstances***

The importance of patients being able to make their own decisions is reflected in the contemporary centrality of ‘patient-centred care’ [60,61]. Properly respecting the values and circumstances of patients does not mean swapping a paternalistic approach for an equally polar norm in which patients have absolute autonomy over all courses of action [62,63]. Nevertheless there is an inevitable imbalance between the clinical expertise of doctors and patients who are experts in their own experience and the subject of the disease and its treatment [64–66]. As such, patient-centred care and prioritisation of outcomes in AD should be conceived as a *collaboration* known as ‘shared decision-making’ [67,68].

Knowledge-related power imbalances underline the ethical importance of remembering that it is the patient who must have the final say. Indeed, this is especially important in the case of AD, where treatment options are limited. For example, if faced with the prospect of cognitive decline a patient may, for example, decide not to accept a pacemaker to prevent heart failure. It is not obvious in such circumstances that the decision against prolonging life as long as possible is either irrational or to be avoided. As van Summeren et al [3] report, a dilemma often faced by patients, carers, and clinicians, is how to balance factors such as the benefit of palliation of symptoms and maintenance of life or independence against the discomfort caused by the side effects of a potentially complicated drug regime. Examples such as this thus remind us of the primacy of the AD patient’s right to choose, even within a shared decision-making model.

### ***Conflicting Priorities***

Complications arise when determining and combining preferences. For example, the difference between qualitative and quantitative findings present a challenge when pooling and attempting to

weigh different forms of evidence [69,70]. To mitigate this, preference elicitation techniques [71–73] exist to help individuals to arrive at a decision or ranking of the various outcomes and permutations.

Ordering outcomes according to their desirability may not be straightforward, given the different ways in which a disease and its symptoms may affect daily living and wellbeing. For example, in patients with multiple conditions or comorbidities, countervailing factors will need to be taken into account [10] to arrive at what is, overall, the best balance between benefits and risks of one approach to treatment rather than another [74,75]. Ordering outcomes is also complex because the ‘best’ balance of risks and benefits may be plural, that is, there may be more than one ‘right’ decision in any given scenario. This is especially pertinent in the AD context, given that no cure is available at present. Were there curative treatments it may be easier to calibrate the relative desirability of different options since, presumably, reversing the disease would be always be prioritised over other outcomes. In the absence of curative treatment, deciding on the ‘right’ course of action must be made by the careful weighing of other, suboptimal, options.

Ethical challenges in outcome prioritisation also emerge when priorities conflict, for example between short- and long-term treatment goals, considering that the development of drugs and tests is slow and resource intensive [76], even when research funding prioritises a particular condition [77]. Moreover, there may be challenges in involving all relevant stakeholders in the prioritisation process [78]. For example, factors such as linguistic barriers and insensitivity to different cultural values mean that minority ethnic groups are under-represented in research [8,79–81].

There may also be intractable conflicts of priorities in relation to decisions concerning the end of life. Qualitative research by Goodman et al (2013) [5] reminds us that for many people with dementia, death may be preferable to a severely impaired life with dementia. Since family members and carers cannot (legally) hasten death to bring an end to unwanted suffering, it is not obvious how such wishes can be meaningfully accommodated.

As Hunter [82] writes, questions about whose responsibility it is to engage in the process of prioritising outcomes are also ethically contentious. This creates a further set of practical ethical

complexities around the balance of duties and responsibilities between patients, carers, society at large, clinicians, policy makers, health economists, and other bodies with a stake in optimising care. For instance, prioritisation can be complex when making choices regarding prevention or disease progression, such as whether to provide treatment to those who are most in need, or those who would benefit the most. There is no straightforward way to resolve dilemmas such as this, which reminds us we cannot assume that priorities will be uniform and agreed between patients, their carers, clinicians, and the wider general public [47,48,83]. Indeed, such dilemmas may be fundamentally unresolvable, given that, ultimately, one group's interests will be relatively de-prioritised.

We can go further still than this to reinforce the point if we keep in mind that allocation dilemmas in a specific context such as AD are not unique in their complexity, since in the vast majority of instances, notwithstanding certain paradigmatically immoral acts such as torture or rape, ethical judgements are always contestable. Since there is no objectively agreed standard of measurement or value as is more readily available in the sciences, it is the nature of moral deliberation that grounds for rational disagreement can never be completely extinguished. Returning to the extant context of health outcome prioritisation in AD, therefore, this general characteristic of ethical discourse underwrites the claim that what counts as a successful decision and legitimate prioritisation of outcomes will consist in the fastidiousness of the process by which the decision was reached in terms of considering the views of as wide a range of stakeholders as possible [84], rather than the decision itself.

### ***Communication, Autonomy and Caregiver Issues***

AD impedes communication [84], cognition [85], autonomous decision-making [86], social participation [87], independence [88] and has a psychological and emotional impact affecting relationships and perceptions of self and personhood [89,90] as the disease progresses from Mild Cognitive Impairment (MCI) onwards [4,48]. This becomes increasingly significant as the disease advances and compromises more aspects of life, as family carers may often need to spend an increasing amount of time supporting their relative with AD and making decisions on their behalf on the basis of what they take to be the relative's wishes [4,91].

Questions of self-determination are immediately relevant in this context. Seeking out the preferences of people with AD and other dementias is crucial as far as it is possible to do so [92] and it is important not to assume that people with dementia are necessarily unable to speak for or represent themselves, albeit that sensitivity and flexibility must be shown to the varying lengths of time that someone with AD may need to make choices or communicate their wishes [93]. For example, at the end of life it is of the utmost importance that the dying person's wishes are understood as explicitly as possible in advance [94–96], moreover, it should not be assumed that people will be unable to express their preferences in some form, even at later stages of the disease or at the end of life [11,97]. This is vital when considering who has a say in determining which outcomes matter: firstly to ensure that those who can contribute do so; and secondly to ensure that first-hand experiences of different disease stages are represented. This is an issue of both fairness – in that there should be no systematic exclusion based on assumptions about capacity at particular stages; and validity - in that the actual priorities of patients are heard above the hypothetical priorities of those imagining being in such circumstances.

The completion of advance directives by individuals before their dementia becomes too advanced to communicate their preferences towards the end of life are one option for negotiating likely future communication issues [98]. However, these are not without potential ethical problems; for example that they are often left incomplete such that the individual's wishes are uncertain or unknown to carers and others [95]; and the validity of advance directives can be disputed or undermined given that it is possible an individual's preferences change after they are no longer able to communicate this to others [92]. As such, when attempting to make prioritisation decisions in the later stages of AD, it is important to keep in mind that advance directives, while undoubtedly a vital tool for eliciting preferences, are nevertheless fallible.

Given the progressive, degenerative nature of AD it can become increasingly difficult to know the priorities and preferences of the person affected. Often, caregivers, whether professional or unpaid, family members, or partners are able to understand the affected person's wishes as their ability to clearly communicate their preferences diminishes [84,99–101]. However, this presents a challenge for



ensuring that carers properly represent the affected person's interests and, crucially, that they respect and protect the dignity of the person with dementia [102]. This is a considerable ethical challenge, as knowing what we ought to do for people with AD if their preferences are only indirectly discernible or require interpretation raises the risk of erroneous decisions. Again, the limitations of advance directives should also be taken into account in relation to this point.

People with AD are vulnerable if they cannot communicate effectively and may be more reliant on their carers to represent their interests. While most carers will do this, it cannot be assumed that all risks of misrepresentation or mistreatment are eliminated [103]. For example, carers' evaluations of the quality of life of people with AD are typically negative [104], but we cannot verify this precisely because of the impaired communication that the disease brings about. Similarly, there is evidence to suggest that carers wish patients to remain in the milder stages for as long as possible and decline rapidly towards the end to minimise the impact that it will have on them, but we cannot assume that this is what the person being cared for would also wish [105]. One reason may be that the burden and risk of isolation experienced by carers increases as the patient's disease progresses, and their judgement of the patient's quality of life can be negatively influenced by the deterioration in their own quality of life [106,107]. Nevertheless, it is important here to consider carers as stakeholders with a legitimate voice of their own regarding outcome prioritisation, separate from the extent to which they can reliably interpret the wishes of those for whom they are caring [108,109].

### ***Disclosure of Risk***

The risk of progressing from MCI to AD may be an important outcome for people in early stages of cognitive decline; however, the uncertainty of such predictions and the limited ability to act on it, make knowledge of one's risk ethically complex. For instance, although preclinical testing for AD is advancing in accuracy and scope [110], understanding the wishes of all those to whom such testing may be relevant is important for harm reduction [111] and ensuring individuals have the greatest scope for decision-making that they wish to have, whatever their decisions and preferences following risk disclosure might be. People identified at high risk of developing AD, such as some MCI patients, will already feature in such considerations, since, as Rose (1985) [112] points out, the best indicator

of major disease in future is often the existing presence of minor disease. Indeed, the current diagnostic guidelines state that AD dementia is preceded by MCI, and MCI is preceded by an asymptomatic preclinical AD phase [113]. However, as algorithms become better at predicting risk in asymptomatic individuals - namely, those who have biomarkers of the disease but no symptoms- those to whom this will become relevant will increase in line with the increasing accuracy of predicting AD at the asymptomatic stage.

In each group deemed at risk, the ethical ramifications of testing centre on how individuals, and those close to them, should respond to risk information as well as what responsibilities fall on those disclosing the risk status. For example, this will extend to family members, as knowledge that a relative will or is likely to develop AD will affect their lives, not least because some of those family members or partners may have to become carers [43,114]. Moreover, in the case of genetic risk factors for AD which can be identified at any age, such as APOE, genetically related relatives may be faced with a decision about whether they too wish to undergo testing for presence of such markers [115].

These scenarios are ethically challenging as long as AD remains incurable. For example, while cognitively normal, asymptomatic, individuals may be able to reduce their risk of developing MCI or AD by making lifestyle changes in mid-life, there is an absence of high-quality, reliable evidence for the effectiveness of these changes, and as such they do not guarantee it [116,117]. As such, it cannot be assumed that individuals will necessarily prioritise receiving risk information in the absence of a guarantee that successful prevention is possible. Nevertheless, there may be benefits to early risk assessment and diagnosis, since it enables patients to more capably make legal and care arrangements and change their lifestyle so that they can maximise the time they have with significant others [118,119] or to make plans to end their lives before dementia makes that impossible.

To the extent that a foundational duty of healthcare professionals is avoiding and preventing harm, it is necessary to keep in mind a broad conception of harm that encompasses not only physical and cognitive impairment caused by the progression of AD, but psychological and emotional damage that may come to people by knowing their risk. It is straightforward to state that individuals are entitled to

be informed of all the findings of their scan, however distressing these might be, if they wish to and understand the implications of what they might be told. However, it should not be *assumed* that, for example, cognitively normal but amyloid positive individuals [13] should automatically be informed of the results of their scan without prior discussion as to the individual's preferences for disclosure [120], as it may cause significant distress even if the information is sought. Indeed, amyloid positive individuals may live to old age [121] or die before developing notable symptoms, either because of another condition or an accident, even though there is a consensus among clinicians that these individuals would have developed dementia had death not intervened first. In these cases, it is important to elicit what an individual's preferences are with respect to AD, relative to other health risks that they face, also taking into account how legal rights to the disclosure of information to individuals are framed in different jurisdictions.

Aside from the harms of the disease, therefore, disclosure may pose a risk of psychological and emotional harm to affected individuals [122], their carers and families, and the interpersonal relationships between them [123]. Finally, for individuals with private health coverage rather than the majority in the European context who depend on state health provision, known information relating to the risk of disease may affect individuals' insurance premiums and coverage and cover if they are obliged to disclose this to insurers [23,64,108,109,124], and the risk of harm that may come from the exploitation of this information by insurers should be taken into account when balancing the priority of potential outcomes. The risks outlined are some of those adduced in arguments against dementia screening [125,126] and help to demonstrate that although an assumption that diagnosis and knowledge of one's condition would and should always be one's priority may look *prima facie* reasonable, when subjected to scrutiny the situation reveals itself too complex for the assumption to be applicable or necessarily beneficial.

## DISCUSSION

Our analysis indicates that the themes identified can be grouped into three larger arrangements of overlapping ethical issues in outcome prioritisation, which we now discuss. We will also make some remarks about what normative approaches might be appropriate for negotiating them; for example, philosophical tools such as differing theories of justice can inform debate and decision-making in arriving at conclusions about how resources should be distributed; and (social) scientific tools such as quantitative and qualitative research methodologies can help to elicit personal perspectives that are required for understanding what outcomes are important to whom, and why. It is important to note here that there are research consortia which draw together and integrate these expertise towards developing fair and equitable methods of outcome prioritisation in AD, such as IMI EU EFPIA ROADMAP [14,127]

The first group of issues relates to the importance of ensuring the adequacy of the procedures according to which finite resources are allocated. For example, if the needs of a certain group of people cannot be met because it would not be cost-effective to do so, then it is important: first, that relevant professionals are trained to give individuals difficult and potentially distressing news; and second, that the commissioning process is thorough and comprehensively justified, with efforts to prevent geographical disparities, or ‘postcode lotteries’ in provision (themes 1, 2, 6, 7). Similarly, procedures for prioritising outcomes must be able to respond effectively to advances in therapy and the consideration of these under whatever protocol for allocation is applied. If it is important to maximise the benefit from available treatments, then it is commensurately important to ensure that potentially beneficial new developments can be incorporated into resource allocation decision procedures. For these kinds of considerations, we adopt the most general, macro-level perspective. Given that due consideration for the correct balance of rights and responsibilities between the state and the individual falls within the purview of ethics, it is here that the philosophical tools derived from understanding competing theories of justice are instructive for negotiating resource allocation and prioritisation dilemmas.

The second set of issues relates to the specific outcomes to be measured and prioritised and how to ensure that those measured are most important and meaningful to relevant stakeholders (themes 3, 4, 5, 7, 8, 9). Prioritisation can only meet the needs and wishes of the affected parties the outcomes valued by the people to whom allocation decisions pertain are known. This may change at different stages of the disease and hence it is important also to have valid and reliable outcome assessment tools to measure the priority outcomes that are appropriate to these different stages. This obviates the need to elicit the preferences of people with AD and their carers, rather than assuming what outcomes are desired and in what order of preference. Moreover, as we pointed out, understanding what outcomes are prioritised and in what order is also complicated in view of the complexity of AD. Medications may have side-effects and / or drug-drug interactions that may affect the overall outcome for a patient, and since AD is largely a disease of old age it is frequently important to take comorbidities into account when attempting to attach a value to a particular outcome and course of action [34]. To the extent that a duty of prioritisation decisions is to optimise outcomes for people with AD, understanding the preferences of these people is a necessary step in discharging that duty. These demands can be met by qualitative and quantitative research methods in the form of interviews, focus groups, surveys, questionnaires, and digital data collection. As such, social science research tools can be usefully employed for seeking out and understanding individual preferences and the reasons behind them.

The careful application of these tools is also valuable for negotiating the third group of ethical challenges, which, like the issue of age-related comorbidities, is highly relevant to AD, and concerns the way in which individual preferences are sought (themes 3, 7, 8). AD can impair the ability of affected people to clearly make and convey their preferences and wishes, and so there is a potential ethical risk in not prioritising outcomes in a way that meets the needs and wishes of those people. Furthermore, given that AD can impair communication, carers may need to make decisions on a patient's behalf, and there may be conflicting accounts of the patient's best interests. Adequate and ethically robust outcome prioritisation processes depend partly on first having identified what is needed by and important to people with AD, and as such the procedures used to elicit this information

must be capable of doing so. Since cost-effectiveness decisions are necessarily utility-driven, unless preferences for outcomes are successfully elicited and appropriately quantified, there is a risk that these important qualitative aspects of AD are lost against the background of the aggregative method by which prioritisation is directed.

## **LIMITATIONS**

This is a non-systematic narrative review. One potential limitation may come from the type of conducted search, where only the titles were searched for presence of keywords. This limitation was mitigated by subsequent snowball sampling of further relevant manuscripts, which significantly increased the number of papers eligible for review. Another potential limitation may come from the single-reviewer process applied to this study at the abstract selection and initial full-text review stages. This limitation was to some extent mitigated by the iterative analysis process, where all contributors reviewed, discussed and contextualized the results, reaching back to the original sources as needed; and by the reviewing of a subset of titles by a co-author and comparison of decisions for inclusion and exclusion. A further limitation is that since we have only used English language studies in this paper, we are unsure of the reliability of our findings for non-English speaking AD communities. However, this was unavoidable given the resources available to the authors.

A final limitation is that since the later stages of editing post-peer review were carried out during the initial lockdown phase of the 2020 Covid-19 pandemic, the authors are unable to review literature about the ethical implications of outcome prioritisation in AD in the context of the current pandemic and potential future ones. Given that the paper is based on a review of the relevant literature, while AD-relevant studies produced in light of the pandemic will undoubtedly emerge, the paper has not been produced sufficiently long after the initial global infection for such material to be published made available for analysis.

Nevertheless, we can make a tentative remark that it would be worthwhile to investigate in future work. It is likely that situations such as the Covid-19 pandemic may change what are considered acceptable trade-offs in outcome prioritisation within the eight themes that we identify in this study. A possible concrete example of this might be accepting the additional safety risks associated with remote monitoring of people with AD living on their own, in order to shield them from the more immediate infectious disease risk that would come with usual levels of face-to-face contact.

## CONCLUSION

Our analysis demonstrates the essential role that ethical deliberation plays in ensuring the just prioritisation of outcomes. Given that discussions about how we ‘should’ allocate resources is an irreducibly normative question, expertise in ethical and philosophical reasoning are indispensable for a task such as this, irrespective of the fact that the task is an applied one and these kinds of expertise are putatively theoretical. Of course, the evidence to which we refer is similarly indispensable, since without empirical information about how and why different stakeholders prioritise outcomes in the way that they do, no rational negotiation of these towards a just outcome can be carried out. Nevertheless, what ought to be done cannot simply be read off these descriptive data. For this reason, allied with the compelling need to find new strategies for managing AD in view of the growing societal pressure that it is exerting, we conclude by reiterating the central role that ethical reflection contributes in decision-making processes regarding the prioritisation of patient outcomes.

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## **Authorship Declaration**

All authors satisfied the following conditions of authorship to a degree commensurate with their position in the ordering of authorship:

Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data.

Involvement in drafting the manuscript or revising it critically for important intellectual content.

Final approval of the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## **Availability of Data and Materials**

Not applicable.

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### **Conflict of Interest / Disclosure Statement**

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Alex Keenan is a full-time employee and shareholder of Janssen Pharmaceuticals and Johnson & Johnson.